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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BAGGOT, BRENDAN O	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/540,063	GEIGENBERGER ET AL.	
	Examiner	Art Unit	
	Brendan O. Baggot	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-14,18,19,23,24 and 45* is/are pending in the application.

4a) Of the above claim(s) *1-3,15-17,20-22 and 25-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14, 18-19, 23-24 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction / Election

1. The Office acknowledges the receipt of Applicant's restriction election, filed 6/21/06. Applicant elects Group II claims 4-14, 18-19, 23-24 and 45, with traverse stating primarily that the general inventive concept is expressing hemoglobin or leghemoglobin to produce altered storage reserve content transgenic plants and that international Examiner found unity of invention "regarding the sequences and the genes". Applicant's traversal is unpersuasive for the following reasons: The cited art, McElroy (6,232,526-US) and Rogers (6,174,724-US), – according to Applicant – ". . . teach[es] genetically engineered plants and . . . hemoglobin" (See p. 8 , Applicants Amendment and Response to Restriction) and therefore necessarily teaches expressing hemoglobin or leghemoglobin to produce altered storage reserve content transgenic plants. Does Applicant suggest that expressing hemoglobin in transgenic plants does not alter the plant storage reserve content?

Claims 1-3, 15-17, 20-22, 25-44 are nonelected. Claim 4-14, 18-19, 23-24 and 45 are pending and examined in the instant application.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This restriction is made FINAL.

Sequence Listing

2. Applicant's computer readable format sequence listing has been entered.

Specification

3. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

Information Disclosure Statement

4. An initialed and dated copy of Applicant's IDS filed 6/22/05, is attached to the instant Office Action.

Claim Objections

5. Claims 4-14, 18-19, 23-24 and 45 are objected to because of the following informalities: Claims 4-14, 18-19, 23-24 and 45 are drawn to non-elected hemoglobin sequences which are different than SEQ ID NO: 5. Appropriate correction is required.

Claim Rejections - 35 U.S.C. §112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 6, 12, 13, 21, 23-24, 45 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

In Claim 6 it is unclear what is being retained in the "derived" hemoglobin from Arabidopsis thaliana. Is it SEQ ID NO: 5? SEQ ID NO: 5 is the DNA sequence of an Arabidopsis thaliana Class I non-symbiotic hemoglobin with a particular O_2 dissociation constant and a particular O_2 association constant. Is the "derived" hemoglobin a Class II, non-symbiotic hemoglobin? Is it a hemoglobin other than the elected SEQ ID NO: 5?

In Claims 6, 12, 13, 21, 23-24 it is unclear how a gene structure is different from a gene sequence. Does applicant mean the primary, secondary or tertiary structure of SEQ ID NO: 5?

In Claim 10, it is unclear what the metes and bounds of "approximately" are.

In Claim 10, "identity" is unclear. Does applicant mean evolutionary identity? Sequence identity? Species origin identity?

In Claim 12, 13, it is unclear whether the recitation "in particular" is intended as a claim limitation.

In Claim 24, gene structure lacks antecedent basis.

In Claim 45, the claim is unclear in that the method fails to recite any positive step.

Clarification and/or correction are required.

Claim Rejections - 35 U.S.C. §112, first paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 10 is rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for SEQ ID NO: 5 or a sequence encoding SEQ ID NO: 6, and a method for producing same, does not reasonably provide enablement for sequences having less than 100% sequence identity to SEQ ID NO: 5 and 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The *Wands* court set forth the enablement balancing test.

> Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the 'claims."

M.P.E.P. § 2164.01(a)

The claims are broadly drawn to any sequences with a mere 70% sequence identity to SEQ ID NO: 5.

Applicants teach only SEQ ID NO: 5 and SEQ ID NO: 6, a Class II non-symbiotic hemoglobin from Arabidopsis thaliana.

Applicants do not teach sequences with a mere 70% sequence identity to SEQ ID NO: 5 having the enzymatic activity of SEQ ID NO: 6, Class I hemoglobins, or symbiotic hemoglobins.

The claims are drawn to any sequence having only 70% nucleic acid sequence identity to SEQ ID NO: 5. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are broadly drawn to any hemoglobin, including both non-symbiotic and symbiotic, and encompass any sequences with as little as 70% sequence identity to SEQ ID NO: 5. The broad language expressly includes mutants and allelic variants, including mutations knocking out the active site and the allosteric regulatory sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most reasonably connected, to practice the invention commensurate in scope with these claims.

Claims reciting less than 100% sequence identity are not enabled because they encompass unspecified base substitutions, deletions, additions, and combinations thereof while retaining the ability to catalyze double bond formation. Neither the state of the prior art nor the Applicant teaches what region(s) of SEQ ID NO: 5 or 6 must be retained for catalytic activity. The claims encompass inoperable embodiments but the specification provided no guidance as to how such inoperable embodiments can be

readily eliminated without undue experimentation. Moreover, while one skilled in the art can readily make mutations to SEQ ID NO: 5 or the sequence encoding SEQ ID NO: 6, further guidance is needed as to what mutations would not ablate enzymatic activity. Applicant provided no working example of any mutant sequences within the less than 100% sequence identity scope which has the asserted activity. Accordingly, the claimed invention cannot be practiced without undue experimentation as commensurate in scope with the claims.

Gene identification via hybridization is unpredictable. Truksa and Qu, in Truksa et al (2002), teach that they could only *suggest* that the described cDNAs were conlinin cDNAs. (See page 144-145, Plant Physiology and Biochemistry, Volume 41, Number 2, 1 February 2003, pp. 7). Truksa's teaching supports a conclusion that putative structural genes isolated by hybridization and which hybridize or which are complementary are not enabled and would require undue experimenation to determine if the hybridizing sequences were in fact structural genes.

In addition, Smith et al (Nature Biotechnology 15: 1222-1223, November 1997) teach that "there are numerous cases in which proteins of very different functions are homologous" (page 1222, the first sentence of the last paragraph). Also, Brenner (TIG 15, 4:132-133, April 1999) discusses the problem of inferring function from homology, stating that "most homologs must have different molecular and cellular functions" (*See* the second full paragraph of the second column of page 132, for example).

It is well established that sequence similarity is not sufficient to determine functionality of a coding sequence. See the teachings of Doerks (TIG 14, no. 6: 248-

250, June 1998), where it states that computer analysis of genome sequences is flawed, and "overpredictions are common because the highest scoring database protein does not necessarily share the same or even similar function's" (the last sentence of the first paragraph of page 2484. Doerks also teaches homologs that did not have the same catalytic activity because active site residues were not conserved (page 248, the first sentence of the last paragraph).

Lazar et al (1988, Mol. Cell Biol. 8:1247-1252) teach that a replacement of aspartic acid at position 47 with an alanine or asparagines in transforming growth factor alpha had no effect, but that a replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Small changes in amino acid sequence can even completely modify enzymatic function; Broun et al (1988, Science 282:1315-1317) teach that a change of four amino acids converts an oleate 12-desaturase to a hydroxylase. Thus Lazaar et al and Broun et al demonstrated that one or a few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

While Applicant is not required to provide working examples of each claimed embodiment, further guidance as to which region of the disclosed sequences can be tolerate mutations while retaining activity is required. Absent such guidance, one skilled in the art would not be able to use the claimed nucleic acid sequences without undue experimentation.

Claim Rejections - 35 U.S.C. §112, first paragraph, written description

8. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim reciting approximately 70% sequence identity lack adequate written description because Applicant does not disclose a representative number of species as encompassed by these claims. The claims encompass mutants and allelic variants and thus imply that structural variants exist in nature, yet no structural variant has been disclosed. The claims also encompass aldehyde reductase polypeptides from other species. The implication is that there is a gene and a protein other than that disclosed which exists in nature, but the structure thereof is not known. Thus, there are insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants, allelic variants and aldehyde reductase polypeptides from other plants and organisms, absent further guidance.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that

material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Finally, the court held:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Id.

See also MPEP Section 2163, page 174 of Chapter 2100 of the August 2005 version, column 1, bottom paragraph, where it is taught that

> [T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021, (Fed. Cir. 1991) where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence).

Given the claim breadth and lack of guidance as discussed above, the specification fails to provide an adequate written description of the genus of sequences as broadly claimed. Given the lack of written description of the claimed genus of sequences, any method of using them, such as transforming plant cells and plants therewith, and the resultant products including the claimed transformed plant cells and

plants containing the genus of sequences, would also be inadequately described.

Accordingly, one skilled in the art would not have recognized Applicant to have been in possession of the claimed invention at the time of filing. *See* The Written Description Requirement guidelines published in Federal Register/ Vol. 66, No. 4/ Friday January 5, 2001/ Notices: pp. 1099-1111.

Claim Rejections - 35 U.S.C. §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 4, 6-14, 20-24 drawn to SEQ ID NO: 5 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Harper (2002 0160378-US, published 10/31/02). Harper teaches a transformed plant (*See* paragraph 137, 164), a vector (paragraph 51) expressing SEQ ID NO: 5 (See paragraph 60; Table 1, p. 45, SEQ ID NO: 1274; Table 1,p. 47, SEQ ID NO: 1539) from Arabidopsis (See paragraph 11). Harper further teaches expressing hemoglobin in an organ specific (See paragraph 99) or tissue specific (See paragraph 96) manner. (See also paragraph 155; Claims 29, 52, 56, 57).

Harper also teaches corn and potato which produce starch and oil. (See paragraphs 155, 56, 160). Accordingly, Harper anticipated the claimed invention.

10. Claims 4, 6 11, and 12 drawn to SEQ ID NO: 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Sowa (1998) PNAS 95: 10317-10321). Sowa teaches a transformed plant expressing hemoglobin from Arabidopsis hemoglobin. (see Figure 2, p. 10318) Sowa also teaches corn which produces starch and oil. (See paragraphs 155, 56, 160). Accordingly, Sowa anticipated the claimed invention.

Claim Rejections - 35 U.S.C. §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The *Graham* court set forth the factual inquiries that are applied for determining obviousness under 35 U.S.C. 103(a):

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.]

Graham v. John Deere Co., 383 U.S. 1.

11. Claims 4, 6-8, 11-14, 45 drawn to SEQ ID NO: 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sowa (1998) PNAS 95: 10317-10321) in view of Arntzen (6395964-US, 6/99).

The teachings of Sowa have been discussed supra.

Arntzen teaches a transformed plant expressing at least one protein (Col. 22 Ln. 10-20; Col 25, Ln. 50-60; Col. 15; Col. 22 Ln. 10-20); transformed plants, including monocots and dicots such as a corn or potato (Col. 11 Ln. 15-16) containing a DNA construct comprising a patatin promoter (Col.26 Ln. 43); plant expression of a protein (Col. 13. Ln. 50-60); a transformed plant expressing one or more proteins (Col. 22 Ln. 10-20; Col 25, Ln. 50-60); tuber specific expression (Col.26 Ln. 43); and seed specific expression (Col. 8 Ln. 25-50); (Cl. 15; Col. 22 Ln. 10-20).

It would have been *prima facie* obvious at the time the invention was made to express the hemoglobin of Sowa in another plant such as potato for the purpose of producing hemoglobin in alternate host systems. Expression of heterologous proteins in different plant hosts, including both monocots and dicots have been successful as evidence by Sowa and Arntzen. It would have been obvious to use different promoters such as seed specific promoters to target expression to a particular organ for

concentrated expression and ease of harvesting the expressed protein. Thus, one skilled in the art would have been motivated to generate the claimed invention with a reasonable expectation of success.

12. Claims 4, 6-14, 20-24, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sowa (1998) PNAS 95: 10317-10321) and Arntzen (6395964-US, 6/99) as applied to Claim 4, 6-8, 11-14, and 45, and further in view of Trevaskis (1997) Proc Natl Acad Sci 94(22):12230-4).

The teachings of Sowa and Arntzen have been discussed supra.

The combination of Sowa and Arntzen does not teach hemoglobin having the sequence of SEQ ID NO: 5.

It would have been *prima facie* obvious at the time the invention was made to express a known hemoglobin sequence such as SEQ ID NO: 5 of Trevaskis for the purpose of producing hemoglobin in plant. Any known hemoglobin sequence known in the art can be expressed without any surprising or unexpected result. Therefore, one skilled in the art would have been motivated to construct an expression vector containing SEQ ID NO: 5 and express it in the plant of Sowa or Arntzen with a reasonable expectation of success.

Remarks

13. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brendan O. Baggot whose telephone number is 571/272-5265. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571/272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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8/31/06

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